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Clearance of an epidemic clone of methicillin-resistant *Staphylococcus aureus* in a drug-use network: A follow-up study in Switzerland

Colombo, Carlo ; Senn, Gabriela ; Bürgel, Anne ; Ruef, Christian

Abstract: Background: A single clone of methicillin-resistant *Staphylococcus aureus* (MRSA) was observed in a drug-use network starting in 1994, and was found to persist throughout 2001, with up to 19% MRSA colonization of intravenous drug users (IDUs). Recent clinical observations have shown low prevalences of this endemic drug clone among MRSA isolates. The goal of this study was to assess the evolution of MRSA carriage among IDUs. Methods: The survey took place from November 2008 to September 2009. Ten drug dispensary facilities took part. Demographic and clinical data including sex, history of MRSA, past hospitalization, use of antibiotics, and presence of wounds were collected. Screening of the nares, throat, and wounds was done. Results: Five hundred and fourteen swab specimens were obtained; 497 of them were nose/throat samples and 17 were wound swabs. MRSA was identified in 5 samples (1%). Four MRSA were found in nose/throat samples and 1 in a wound swab. Pulsed-field gel electrophoresis typing of the MRSA isolates revealed 2 different common endemic types: 4 were identified as the Zurich IDU clone and 1 as the Grison clone. Conclusions: The study shows a significant decline of MRSA colonization among IDUs. The underlying causes for this decline could not be determined fully, but we hypothesize a bundle of interventions as contributing: enhanced medical care, better wound management, isolation management, teaching IDUs basic hygiene techniques, and the national 'Four Pillars' policy. Hospital epidemiological policies such as pre-emptive isolation, length of isolation time, and screening procedures were adapted accordingly.

DOI: <https://doi.org/10.3109/00365548.2012.672766>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-63727>

Journal Article

Accepted Version

Originally published at:

Colombo, Carlo; Senn, Gabriela; Bürgel, Anne; Ruef, Christian (2012). Clearance of an epidemic clone of methicillin-resistant *Staphylococcus aureus* in a drug-use network: A follow-up study in Switzerland. *Scandinavian Journal of Infectious Diseases*, 44(9):650-655.

DOI: <https://doi.org/10.3109/00365548.2012.672766>

**Clearance of an epidemic clone of Methicillin-resistant *Staphylococcus aureus* in a drug-use network:
a follow-up study in Switzerland**

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Keywords: drug users, epidemic clone, MRSA, prevalence, public health

Running title: Significant decline of epidemic MRSA in a drug use network

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Conflict of interest: All authors no conflict

Financial support: None declared

Abstract

Background: A single clone of MRSA has been observed in a drug-use network since 1994 and persisted throughout 2001, with up to 19% MRSA colonization of intravenous drug users (IDU). Recent clinical observations showed low prevalences of this endemic drug-clone among MRSA isolates. The goal of this study was to assess the evolution of MRSA carriage among IDU. *Methods:* The survey took place from November 2008 to September 2009. Ten drug dispensary facilities took part. Demographic and clinical data included sex, history of MRSA, past hospitalization, use of antibiotics, presence of wounds. Screening of nares, throat and wound was done. *Results:* 514 swab specimens were obtained. 497 of them were nose/throat samples, 17 wound swabs. MRSA was identified in five samples (1%). Four MRSA were found in nose/throat samples, one in a wound. PFGE typing of the MRSA isolates revealed two different common endemic types: four were identified as the Zurich IDU clone and one as the Grison clone; one sample could not be typed. *Conclusions:* The study shows a significant decline of MRSA colonization among IDU. The underlying causes for this decline could not be determined fully, but we hypothesize a bundle of interventions as contributor: enhanced medical care, better wound management, isolation management, teaching iv-drug users basic hygiene technique, the national 'Four Pillar' policy. Hospital epidemiological policies such as preemptive isolation, length of isolation time and screening procedures were accordingly adapted.

Introduction

Staphylococcus aureus is a major cause of soft tissue infection among intravenous drug users (IDU) [1-4]. The rate of *Staphylococcus aureus* carriage among iv-drug users is higher compared to the general population [5-7]. Emergence of MRSA among IDU and clusters of MRSA in the population of drug users has been reported from the US, Canada and the UK [8-10]. In Switzerland the appearance and spread of a single clone of MRSA in a drug-use network has been observed starting in 1994 [11]. Its persistence has been documented in 2001, with up to 19% of IDU colonized by MRSA [12]. The transregional dissemination of this single clone indicated the capacity for spreading and colonizing other drug-use networks [13]. This clone belongs to the sequence type ST45 (Berlin-clone) and has a novel *SCCmec* cassette [14, 15]. Based on the high prevalence of this particular clone among IDUs in Zurich and its epidemic circulation in several hospitals in Zurich, infection control measures were preemptively taken upon admission of persons with a history of intravenous drug use. Over the past years healthcare institutions in Zurich and surrounding communities observed fewer patients (IDUs and non-IDUs) with infections caused by this endemic drug-clone. This was observed in particular at the University Hospital of Zurich as the main clinical and surveillance center for this IDU clone with a decline of the yearly rates of clinical samples for the IDU clone per number of admissions. A decline of MRSA infections has recently also been reported from the United States and Europe [16, 17].

The goal of this study was to assess the prevalence of MRSA carriage in the population of intravenous drug users in order to obtain updated information on the evolution of MRSA in this setting, in particular the evolution of the epidemic clone.

Methods

Surveillance and clinical setting

This epidemiological study is a follow-up of the previous point prevalence surveys conducted in 1999 and 2001 [11, 12]. It took place between November 2008 and September 2009. A hospice with a dispensary

(Sune-Egge), two facilities that distribute drugs and allow injection of drugs under controlled circumstances (Crossline and Lifeline), four drug-injection facilities (Kontakt & Anlaufstellen, K&A), two methadone and heroin-assisted outpatient clinics (Zokl I and Zokl II) and one institution for homeless and persons with drug problems (Ur-Dörfli) participated in the study. These institutions were frequented by 2070 persons with current active intravenous drug use, a history of intravenous or other form of illicit drug use that were in a substitute program in 2009. Some individuals visited several institutions consecutively. The same institutions participated in the study in 1999, with an estimated similar proportion of participating persons. All except one institution are located in the centre of Zurich. The participation of the study attendees was voluntary and anonymous. Persons visiting the institutions on a given day were invited to participate. Participants gave oral informed consent to the chief medical administrator of each institution.

Demographic data included age and sex. Clinical data included history of MRSA, hospitalization within the last year, use of antibiotics during the last seven days and presence of current wounds. This information was obtained during a structured interview. The participants were not examined clinically.

Microbiological studies

Screening of both nares (one swab for both nares) and throat was done with sterile moisturized swabs. These two swabs were pooled. Samples were taken of wounds in the case of an open wound being present.

Nose/throat and wound swabs were immediately introduced into transport medium (Stuart medium). Swabs were inoculated into tryptic soy broth (TSB) (BBL, Cockeysville, MD, USA) containing 6.5% NaCl and, after 24 hours, subcultured on Chromagar *Staphylococcus aureus* (MRSA ID, BioMerieux, France) at 35 degrees C. The subcultures were examined after 18-24 hours. Suspicious colonies were identified as *S. aureus* by catalase production, positive clumping test, or positive tube coagulase test. MRSA was confirmed by oxacillin and ceftioxin disk diffusion susceptibility testing according to CLSI guidelines [18] and isolates were additionally confirmed with MRSA-Screen (Denka Seiken), a slide latex agglutination kit for the rapid detection of penicillin-binding protein 2 (PBP'2). Molecular analysis of each isolate was done by pulsed-field gel electrophoresis (PFGE) with the use of *Sma* 1 restriction enzyme, by use of a CHEF-DR III system (Bio-Rad) as previously described [11]. Banding patterns of restriction fragment bands were analyzed using Gel Compare software. In contrast to the 1999 and 2003 study, we did use selective agar for MRSA and therefore did not test for Methicillin susceptible *Staphylococcus aureus*.

Data Analysis

Data were analyzed using STATA 10.0 (Stata Corp, College Station, Texas, USA). Chi-square test was used to analyze categorical variables. Student's t-test, Kruskal-Wallis test were used for the analyses of continuous variables. A p-value of less than 0.05 was considered significant.

Results

Demographics

In this point prevalence study we evaluated 497 individuals and obtained a total of 514 swab specimens. Of the 497 tested individuals, 392 (78.9%) were males, 105 (21.1%) females (Table I). Overall median age of the test persons was 41 years (range 18 to 60 years), of males 42, of females 40, respectively. Highest median of 44 years was in the hospice specialized in palliative care. The median age of the study population increased significantly from 34 years in 1999 to 41 years ($p < 0.001$) in the present study.

Clinical results

156 persons (31.4%) reported hospitalization during the year prior to sampling, of which 22 were hospitalized in medical institutions outside of Zurich. This rate is significantly lower than the rate of 57.6% observed during our prevalence study conducted in 1999 ($p < 0.001$). Four persons were hospitalized in psychiatric clinics, 152 persons in other hospitals and primary care centers.

Although 60 persons (12.1%) of the present study reported to have a current or chronic wound, only 17 wound swabs were taken for testing. Antibiotic use during the last seven days prior to the time of sampling was reported by 43 persons (8.6%). In the majority of cases amoxicillin/clavulanic acid was used, in some cases sulfamethoxazole/ trimethoprim, clindamycin or fusidic acid.

MRSA

Seven persons declared to be or to have been carriers of MRSA in the past. Three persons reported that MRSA was treated and eradicated. We obtained 497 nose/throat samples (96.7%) and 17 wound swabs (Table I). Methicillin-Resistant *Staphylococcus aureus* was identified in five samples (1%). Four MRSA were found in nose/throat samples. One of these IDUs was previously known to be MRSA positive (case 1). MRSA was found in the wound of another patient, who also was previously known to be colonized with MRSA (case 5). PFGE typing of the MRSA isolates revealed two different common endemic types: four isolates were identified as the Zurich IDU clone [14] and one as the Grison clone [13] (Table II, Figure 1). Fisher's exact test revealed no

statistical differences between MRSA positive persons and MRSA negative persons concerning age, sex, presence of wounds, and consumption of antibiotics, or hospitalization. Comparison of the screening results from the hospice Sune-Egge alone showed a significant decline of positive MRSA samples as well (Table III).

Discussion

Our study shows a decrease of the prevalence of MRSA colonization among users of intravenous drugs in Zurich. The endemic Zurich MRSA IDU clone, which has spread to other regions and has previously been involved in nosocomial transmission to patients not belonging to the drug using cohort, has almost disappeared from the Zurich drug-use network.

An association between *Staphylococcus aureus* carriage among drug users and contaminated needles, or other paraphernalia, has been described in other instances [8, 19]. Drug-use behavior and social organization of drug use, poor hygiene, close personal contact and frequenting the same drug dispensaries or shooting galleries likely facilitate transmission of MRSA [11, 12, 20]. The link between drug-use, frequenting various dispensaries and the prevalence of MRSA in Zurich was substantiated earlier [11]. The prevalence of a single MRSA clone in 1999 was 10.3% among 224 tested IDU's and 30% in the presumed epicenter of the epidemic, a hospice for palliative care. We documented the persistence of a high endemicity of the IDU drug clone in a follow-up study in 2001 with rates of 18.9% overall and 40.9% among patients (IDUs and non-IDUs) (Table III) [12].

Our present study shows a significant decrease of the MRSA colonization rate to 1% overall but also to 1% within the hospice for palliative care. In the first study (1999) we found a wide range of prevalence of MRSA among the different facilities, ranging from 0% in a suburban area and to 28.6% in downtown facilities. In the present study, which covered the same drug dispensary centers, this difference is no longer present.

It is notable, that in the first (1999) and second (2001) study only nose swabs were taken and no selective enrichment broth method was used. In the present study we conducted simultaneous sampling of anterior nares and throat, pooled swabs and used a selective enrichment broth method. Enrichment enhances the sensitivity [21, 22], which may further be improved by pooling of samples [23, 24]. Our results therefore, finding only a few positive MRSA-samples, provide strong evidence for a substantial decline of MRSA prevalence in this cohort of IDU.

The clearance of the previously endemic MRSA clone in Zurich to a sporadic occurrence is impressive, although the cause for this evolution is not totally understood. There are probably several reasons that might explain this positive evolution. Over the course of the last ten years, the mean age of the population of

intravenous drug users in Zurich increased by 6 years to slightly over 40 years. In parallel, a change in drug consumption behavior within the adult population, with street drugs such as injecting heroin being more and more replaced by so-called 'party drugs' like ecstasy, cocaine and others has been observed in Zurich during the last fifteen years [25]. Currently, fewer first time users of intravenous drugs are observed in Zurich and elsewhere in Switzerland [26].

A significantly lower proportion of study participants require hospitalization. At the same time, a diminished incidence of superficial and severe wound infections has been observed. This may be the result of a wider use of local antibacterial ointments (nose/throat, body wash, and wound disinfectants) leading to MRSA elimination in IDUs with less severe and localized wounds [27, 28].

Finally, it can be speculated that a change of policy in Switzerland with an emphasis on a so-called 'Four-pillar' [29, 30] approach to deal with the once widespread drug problem, has had a positive impact particularly in Zurich on the quality of life of people cared for by the drug network. This 'Four-Pillar' policy consists of preventing people from starting consuming (illicit) drugs, treatment of illicit drug related illnesses, installation of substitution programs and finally, law enforcement to control illegal dealings and other criminal activities. This approach has created a safer environment; reducing unclean and unsafe activities, such as exchanging paraphernalia's or living outdoors and consuming drugs under 'dirty' conditions. This is also reflected in the trend towards reduced hospitalization rates and probably has contributed to an increase of the mean age of persons in the iv-drug-network [27].

Based on the findings of our study, hospitals in Zurich have been able to reassess their policy on preemptive isolation of persons admitted with a history of intravenous drug use. Given the currently much lower prevalence of MRSA among this persons cohort, standard precautions combined with MRSA-screening on admission are now used by Zurich hospitals. This change of policy away from preemptive contact isolation has allowed hospitals, psychiatric clinics, first aid ambulance services and other medical institutions to manage admissions and placements more efficiently. Likewise, it puts hospitalized persons under less restriction of movement and reduces stress. Furthermore, fewer isolations of hospitalized persons save time for the medical staff and reduce cost [31, 32].

This study has several limitations. First, not all persons were screened which visited the centres, based on voluntary participation and the point prevalence setting. Second, we conducted a limited amount of wound screening in our present study, even though more persons reported wounds or a history of wounds. Comparability of the present survey with the preceding surveys has a limitation in that we did not screen for wounds in the former studies. In contrast to that, the change of screening method in pooling samples and including wounds has heightened the sensitivity in finding MRSA.

In summary, our findings of a major reduction of the prevalence of MRSA colonization among users of intravenous drugs and persons in drug substitution programs in Zurich over the course of the last nine years are impressive. The potential underlying causes for this decline, such as specific medical, infection control or preventive interventions and their respective contribution could not be determined fully. We hypothesize that the following bundle of interventions has contributed to the current positive situation: improved access to healthcare, better wound management in outpatient clinics and drug dispensaries, isolation management, teaching basic hand hygiene technique and surface disinfection, as well as the 'Four Pillar' policy. Hospital infection control policies such as preemptive isolation, duration of isolation and screening procedures were adapted based on the current findings and the current non-endemicity of MRSA in Zurich's iv-drug-network scene.

Acknowledgments

We thank Drs. R. Zink, P. Bruggmann, A. Moldovanyi and M. Gurguska of the collaborating hospice, drug-dispensary and drug-injection facilities for their helpful cooperation and the participation of their institutions.

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Tables

Table I. Distribution of samples in different test centers and screening results (n=514)

Test center	Sex		Number of nose / throat	Number of wound samples	MRSA positive (%)
	m	f			
Dispensary Zokl I ^a	33	11	44	3	1 (2.1)
Dispensary Zokl II ^a	44	34	78	2	1 (1.2)
K&A ^b Brunau	37	9	46	2	-
K&A ^b Oerlikon	40	12	52	-	2 (3.8)
K&A ^b Kaserne	35	15	50	3	-
K&A ^b Selnau	28	10	38	1	-
Home Ur-Dörfli ^c	18	5	23	3	-
Dispensary Crossline ^d	34	8	42	2	-
Dispensary Lifeline ^d	23	4	27	1	-
Hospice Sune-Egge ^e	70	27	97	Not done	1 (1.0)
Inpatients	31	28	59	-	-
Total	362	135	497	17	5 (1.0)

^a Zokl I and Zokl II: methadone and heroin-assisted outpatient clinics.

^b K&A: drug-injection facilities.

^c Ur-Dörfli: institution for homeless and persons with drug problems.

^d Crossline and Lifeline: facilities that distribute drugs and allow injection of drugs under controlled circumstances.

^e Sune-Egge: hospice with a drug dispensary.

Table II. Demographic and clinical data of the MRSA-positive persons (n=5)

Case	Sex	Age	Wound	Antibiotics last 7 days	Hospitalization last year	Localization of MRSA colonization	MRSA Clone type ^f	Strain numbe
1	Female	21	Yes	No	Yes	nares / throat	IDU Grisons	2717
Zokl I ^a								
2	Male	32	No	No	No	nares / throat	IDU Zurich	2723
Zokl II ^a								
3	Male	45	No	No	No	nares / throat	IDU Zurich	3111
K&A ^b								
4	Female	34	No	Yes	No	nares / throat	IDU Zurich	2754
K&A ^b								
5	Male	41	yes	Yes	Yes	wound	IDU Zurich	2573
Sune-Egge ^e								

^a Zokl I and Zokl II: methadone and heroin-assisted outpatient clinics.

^b K&A: drug-injection facilities.

^e Sune-Egge: hospice with a drug dispensary.

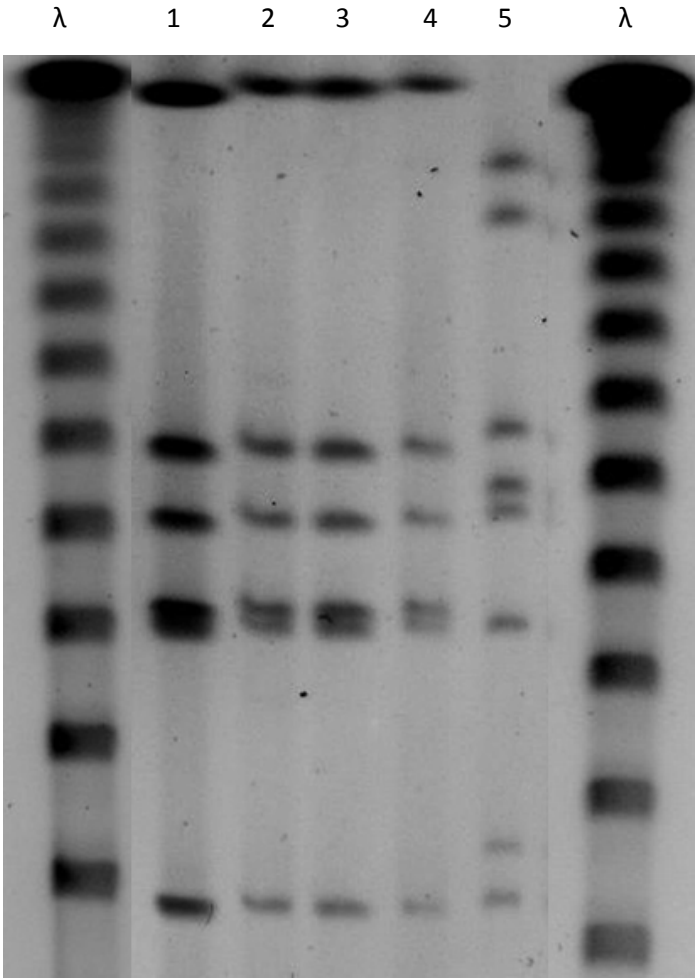
^f IDU Grisons refers to a clone with a high prevalence among intravenous drug users in the Canton of Grisons in Eastern Switzerland [13]. IDU Zurich refers to the clone, which we described in [11] and has become endemic among intravenous drug users in Zurich

Table III. Number of screenings and number of MRSA-positive samples, overall and in the Sune-Egge

Year	Overall		Sune-Egge	
	Number of Screenings	Positive for MRSA (%)	Number of Screenings	Positive for MRSA (%)
1999	224	23 (10.3)	50	9 (18.0)
2001	-	-	53	10 (18.9)
2009	497	5 (1.0)	97	1 (2.2)

Figure 1. Pulsed - field gel electrophoresis (PFGE) profiles of *Sma*I macrorestriction fragments of Methicillin-resistant *Staphylococcus aureus* (MRSA) strains of the MRSA-positive persons

Figure 1.



λ	Lamda ladder
1	2573 MRSA IDU Zurich
2	2723 MRSA IDU Zurich
3	2754 MRSA IDU Zurich
4	3111 MRSA IDU Zurich
5	2717 MRSA IDU Grison
λ	Lamda ladder